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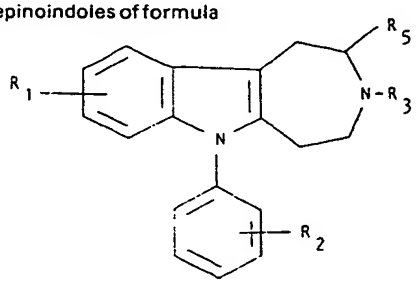
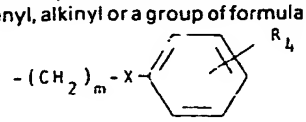
(54) **Azepinoindoles, process for their production and pharmaceutical compositions containing them, and intermediates.**

(57) Azepinoindoles of formula



wherein
R_1 and R_2 are hydrogen, halogen, aklyl, alkoxy, alkylthio, hydroxy, or trifluoromethyl, R_3 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkinyl or a group of formula



wherein
m is 1, 2 or 3,
R_4 is halogen, alkyl, alkoxy, or trifluoromethyl, and alkyl, alkoxy, or trifluoromethyl, and
X is a bond, -CHOH- or -CO-,
or a group of formula

$$-(CH_2-CH_2-O)_nH$$

wherein
n is 2 or 3, and
R_5 is hydrogen or alkyl, are useful neuroleptic, antidepressant and anti-allergic agents.

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see front page

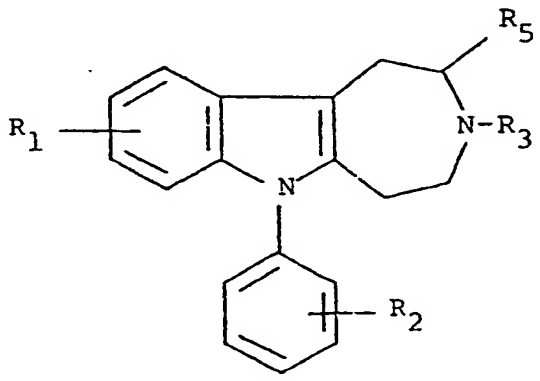
Case 500-5526

NEW AZEPINCINDOLES, THEIR PRODUCTION AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

This invention relates to azepinoindoles, their production and pharmaceutical compositions containing them.

The present invention provides 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b]indoles or pharmaceutically acceptable acid addition salts thereof hereinafter referred to as compounds of the invention. It is to be appreciated that the compounds of the invention may be optionally substituted in any position.

In particular the present invention provides an azepinoindole of formula I,

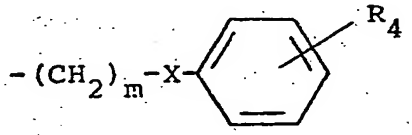


I

wherein

R_1 and R_2 are each independently hydrogen, halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})-alkoxy, (C_{1-4})alkylthio, hydroxy, or trifluoromethyl,

R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl, (C_{4-9})-cycloalkylalkyl, (C_{3-5})alkenyl, (C_{3-5})alkinyl, a group of formula II,



II

wherein

m is 1, 2 or 3,

R_4 is halogen of atomic number from 9 to 35, (C_{1-4})-alkyl, (C_{1-4})alkoxy, or trifluoromethyl, and

X is a bond, -CHOH- or -CO-,

or a group of formula III,

$$-(CH_2-CH_2-O)_nH \qquad \text{III}$$

wherein

n is 2 or 3, and

R_5 is hydrogen or (C_{1-4})alkyl.

In formula I R_1 is preferably in position 8 or 9 of the nucleus. R_2 is preferably in the para position of the phenyl ring. Halogen is preferably chlorine or fluorine and especially fluorine. Alkyl, alkylthio, and alkoxy have preferably 1 or 2 carbon atoms, and

especially 1 carbon atom. Alkenyl and alkinyl preferably have 3 or 4 carbon atoms, especially 3 carbon atoms. m is preferably 2 or 3. When R_3 is a radical of formula II, R_4 is preferably in the ortho or para position of the phenyl ring.

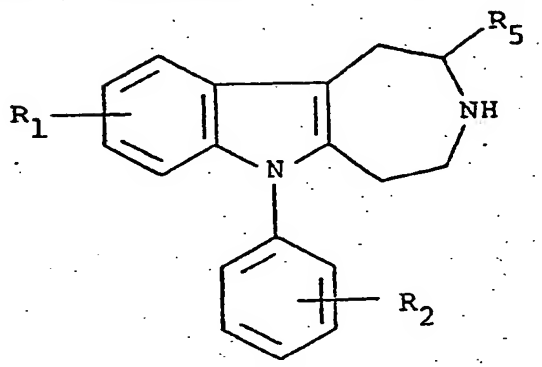
The present invention in another aspect provides a process for the production of a compound of the invention which comprises

i) treating a 1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]-indole having a chloromethyl or bromomethyl group in the 1 position and unsubstituted on the nitrogen atom in the 2 position, with a complex hydride to obtain a 1,2,3,4,5,6-hexahydro-6-phenyl-azepino [4,5-b]indole unsubstituted on the nitrogen atom in the 3 position, and, optionally,

ii) interconverting the 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b]indole into another 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b]indole, e.g. by alkylating the amino group in the 3 position or splitting any ring alkoxy groups to produce hydroxy groups.

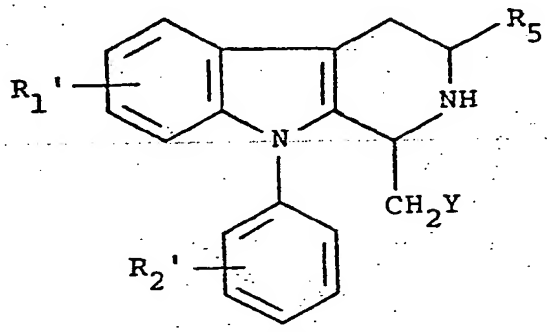
In particular a compound of formula I as defined above may be produced by a process which comprises

a) obtaining a compound of formula Ia,



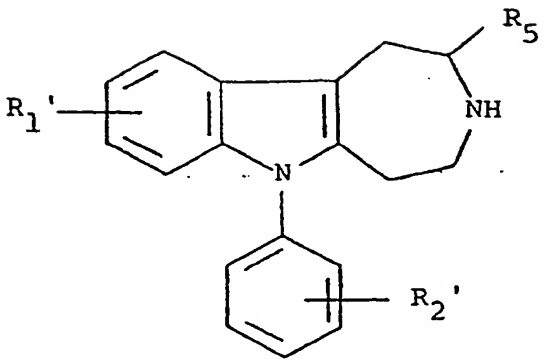
Ia

wherein R_1, R_2 and R_5 are as defined above, by enlarging the six-membered nitrogen containing ring of a compound of formula IV,



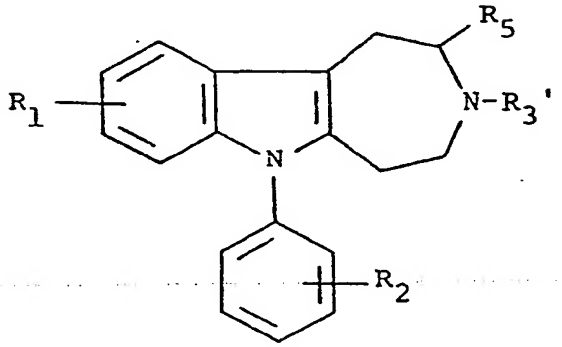
IV

wherein R_5 is as defined above, and R_1' and R_2' have the same significance as R_1 and R_2 except that any hydroxy group present is protected by a hydrogenolytically splittable group, and Y is chlorine or bromine, and when at least one of R_1' and R_2' is a hydroxy group protected by a hydrogenolytically splittable group, hydrogenating the resulting compound of formula V,



V

b) obtaining a compound of formula Ib,



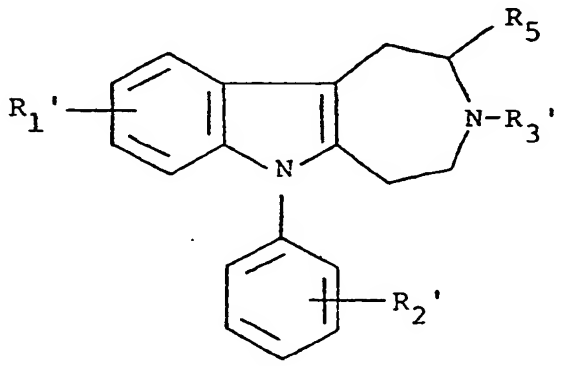
Ib

wherein

R_1, R_2 and R_5 are as defined above, and

R_3' is as R_3 with the exception of hydrogen,

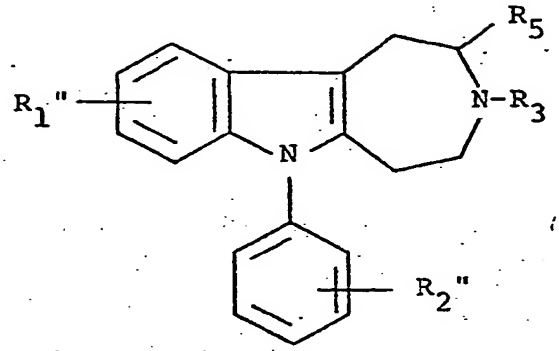
by introducing the group R_3' into a compound of formula V as defined above, and when at least one of R_1' and R_2' is a hydroxy group protected by a hydrogenolytically splittable group, hydrogenating the resulting compound of formula VI,



VI

or

c) obtaining a compound of formula Ic,



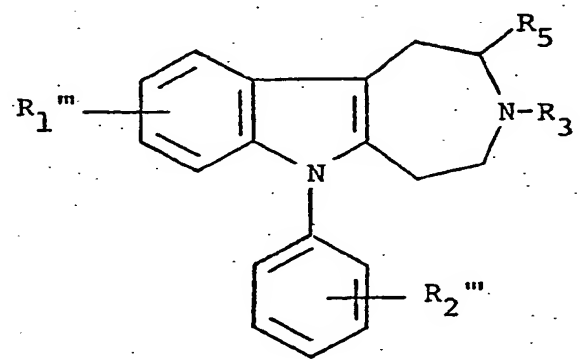
Ic

wherein

R_1" and R_2" have the same significances as R_1 and R_2 with the proviso that (i) none of them is an alkoxy group and (ii) at least one of them is a hydroxy group, and

R_3 and R_5 are as defined above, with the proviso that, when R_3 is a group of formula II, R_4 is other than alkoxy,

by subjecting a compound of formula VII,



VII

wherein

R_1"' and R_2"' have the same significances as R_1 and R_2 with the proviso that at least one of them is alkoxy,

R_3 and R_5 are as defined above, with the proviso that when R_3 is a group of formula II, R_4 is other than alkoxy,

to an ether splitting.

Process i) or a) is conveniently effected in an inert organic solvent, e.g. a cylcic or aliphatic ether, preferable dioxane or tetrahydrofuran. Suitable temperatures are from about 20° C to the reflux temperature, preferably about 60° C. The complex hydride is conveniently aluminium hydride, sodium borohydride or lithium aluminium hydride. When at least one of R_1 and R_2 is chlorine, it is preferred to use aluminium hydride or sodium borohydride.

Benzyloxy is used as the preferred protected hydroxy group.

The splitting off of the protecting group in formula V may be effected in conventional manner, e.g. by catalytic hydrogenation using a palladium catalyst.

The catalytic hydrogenation may be effected in an appropriate solvent, e.g. ethanol. Suitable temperatures are from about 0° C to about 40° C.

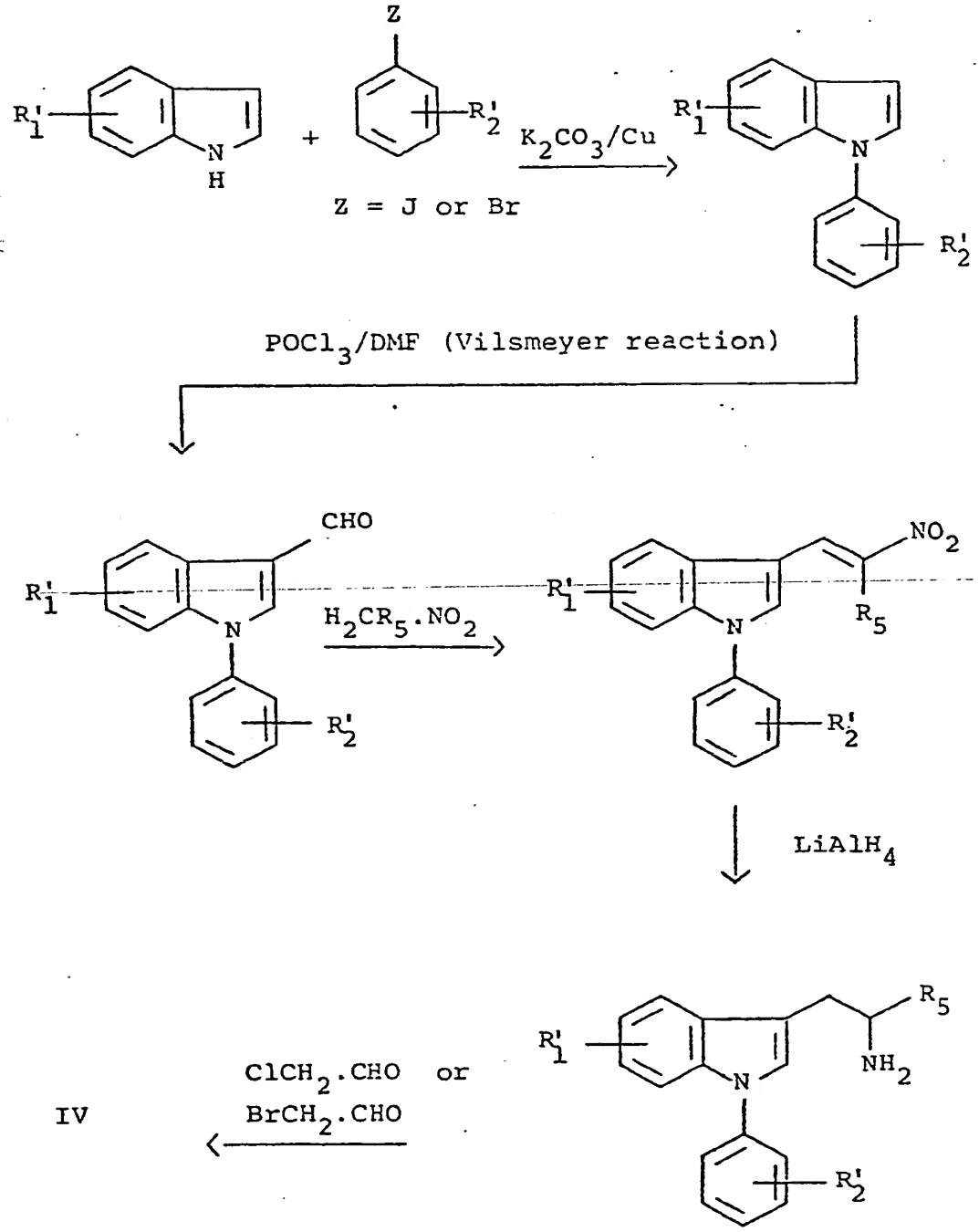
The alkylation reaction of process b) may be effected in conventional manner for the alkylation of an analogous secondary ring amine. As alkylating agent may be used reactive derivatives of a compound of formula $R_3'OH$, e.g. a halide ester or a sulphuric acid deriva-

tive. When R_3' is an alkyl group or a substituted alkyl group such as cycloalkylalkyl, wherein the α-carbon atom bears a hydrogen atom, then an appropriate aldehyde or ketone may be used in the presence of an appropriate reducing agent, e.g. fromic acid.

The catalytic reduction may be effected in analogous manner to that mentioned above.

The process according to reaction c) may be effected in conventional manner for an ether splitting to form hydroxy groups. The reaction may be effected using for example hydrogen iodide, hydrogen bromide, hydrogen chloride. Suitable temperatures are from room temperature to about 100° C. An organic solvent such as acetic acid may be present. Additionally borontribromide may be used as the ether splitting agent. Suitable temperatures are from about -60° C to room temperature. Dichloromethane may be used as organic solvent.

A starting material of formula IV may by obtained for example by as follows:-



Insofar as the preparation of any particular starting material is not particularly described, this is known or may be made in known manner or in a manner analogous to the processes described herein.

Free base forms of the compounds of the invention may be converted into acid addition salt forms in conventional manner and vice versa. Suitable acids for salt formation include hydrochloric acid, fumaric acid, oxalic acid.

In the following Examples all temperatures are in degrees Centigrade and are uncorrected.

In the table the following abbreviations are used:-

1) hydrochloride

2) hydrogen fumarate

3) hydrogen oxalate

4) decomposition

5) oxalate

EXAMPLE 1: 1,2,3,4,5,6-Hexahydro-6-phenylazepino [4,5-b]indole (process a)

A cold solution of 9.5 ml sulphuric acid monohydrate in 200 ml tetrahydrofuran is added dropwise to a suspension of 35.6 g lithium aluminium hydride in 1500 ml tetrahydrofuran at -10°. The mixture is warmed to 60° and a suspension of 79.2 g 1-chloromethyl-1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]indole hydrochloride in 200 ml tetrahydrofuran is added dropwise. The mixture is then warmed for a further 45 minutes, cooled to 0° and the reaction mixture treated dropwise with a saturated sodium sulphate solution. The precipitate is filtered off and washed with ether. The filtrates are concentrated at reduced pressure, and the title compound crystallizes out, m.p. 108-111° (from ether/pentane). M.p. hydrochloride 220-224° (from ethanol/ether).

The starting material 1-chloromethyl-1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]indole may be obtained as follows:-

a) 120 g 1-phenylindole-3-carboxaldehyde and 16.2 g ammonium acetate are heated under reflux in 406 ml nitromethane for 5 hours. The mixture is cooled, diluted with ether to give 3-(2-nitroethenyl)-1-phenylindole, m.p. 154-155°.

b) A suspension of 109.2 g 3-(2-nitroethenyl)-1-phenylindole in 990 ml tetrahydrofuran is added dropwise at 20° to 43.5 g lithium aluminium hydride in 570 ml tetrahydrofuran. The mixture is heated at 60° for 20 minutes. The reaction mixture is cooled. A saturated sodium sulphate solution is added dropwise at -10° C. The mixture is filtered and the precipitate washed with ether. The filtrate is concentrated and the residue, 3-(2-aminoethyl)-1-phenylindole, is converted into the hydrochloride, m.p. 216-220° (from ethanol/ether).

c) 55.6 ml chloroacetaldehyde (45 % in water) are added dropwise to 87.2 g 3-(2-aminoethyl)-1-phenylindole, 400 ml 2N hydrochloric acid and 2.5 litres water at 50°. The mixture is heated for 1 hour at 95°, treated once more with 55.6 ml chloroacetaldehyde and heated for a further 45 minutes. The mixture is then cooled to 0°, made alkaline with conc. ammonia and shaken with ether. The organic phase is dried over sodium sulphate, and purified with animal charcoal, and concentrated. The residue 1-chloromethyl-1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]indole is converted into the hydrochloride, m.p. 174-180° (from ethanol/ether).

EXAMPLE 2: 1,2,3,4,5,6-Hexahydro-3-methyl-6-phenylazepino[4,5-b]indole (process b)

19.8 ml of a 35 % formaldehyde solution and a spoonful of Raney-Nickel are added to 20.4 g 1,2,3,4,5,6-hexahydro-6-phenylazepino[4,5-b]indole in 385 ml ethanol. The mixture is hydrogenated at room temperature. The mixture is then filtered and the filtrate concentrated to give a residue which is partitioned between ether and water. The ether phase is dried over sodium sulphate and concentrated to give the title compound as an oil which is converted into the hydrochloride, m.p. 236-238° (from ether/ethanol).

EXAMPLE 3: 3-Allyl-9-fluoro-6-p-fluorophenyl-1,2,3,4,5,6-hexahydro-azepino[4,5-b]indole

3.1 ml allyl bromide are added dropwise to 9.0 g of 9-fluoro-6-p-fluorophenyl-1,2,3,4,5,6-hexahydro-azepino[4,5-b]indole and 9 g potassium carbonate in 90 ml dimethylformamide. The mixture is stirred for 2 hours at 110° C, cooled to room temperature, poured onto water, and extracted with ether. The ether extracts are concentrated to give the title compound as a residue. M.p. of the hydrochloride 228-238° (decomp.).

EXAMPLE 4: 9-Fluoro-6-p-fluorophenyl-1,2,3,4,5,6-hexahydro-3-methyl-azepino[4,5-b]indole

8.7 ml of a 35 % formaldehyde solution are added dropwise to a solution of 9 g of 9-fluoro-6-p-fluoro-

phenyl-1,2,3,4,5,6-hexahydro-azepino[4,5-b]indole in 6.9 g formic acid. The mixture is heated for 10 minutes to 70°, cooled, poured onto water, made alkaline with concentrated ammonia and extracted with ether. The ether extracts are dried over sodium sulphate and concentrated to give the title compound in hydrochloride form, m.p. 215° (decomp.; from ether/acetone).

EXAMPLE 5: 1,2,3,4,5,6-Hexahydro-9-hydroxy-3-methyl-6-phenylazepino[4,5-b]indole (process c)

A solution of 3.58 g of boron tribromide in 10 ml dichloromethane is added dropwise at -60° to a solution of 2 g 1,2,3,4,5,6-hexahydro-9-methoxy-3-methyl-6-phenylazepino[4,5-b]indole in 20 ml dichloromethane. The mixture is stirred at -60° for 1 hour and a dark oil separates out. The mixture is concentrated under reduced pressure and the residual oil is treated with 30 ml ethanol. The mixture is brought to reflux over 30 minutes and the hydrobromide of the title compound crystallies out. The salt is then filtered off, washed with a little alcohol and partitioned between dichloromethane and aqueous ammonia to form the free base. The organic phase is separated off, washed with water, dried over sodium sulphate, filtered and concentrated under reduced pressure. The oily residue is dissolved in alcohol, treated with hydrochloric acid in ethanol to form the title compound in hydrochloride form, m.p. 290-292° (decomp.).

The following compounds of formula I are produced wherein:-

Ex.	R_1	R_2	R_3	R_5	m.p.	Analogous to Ex.
6	9-CH_3	p-CH_3	H	H	242[1)]	1
7	9-F	p-F	H	H	198-205[1)]	1
8	10-Cl	H	H	H	136-138	1
9	9-Cl	H	H	H	128-130	1
10	8-Cl	H	H	H	oil	1
11	9-OCH_3	H	H	H	oil	1
12	9-Cl	p-F	H	H	oil	1
13	9-Cl	p-Cl	H	H	oil	1
14	H	H	H	CH_3	oil	1
15	9-Cl	p-F	H	CH_3	oil	1
16	9-CH_3	p-CH_3	CH_3	H	270[1)4)]	2, 4
17	10-Cl	H	CH_3	H	282[1)4)]	4
18	9-Cl	H	CH_3	H	258-260[1)4)]	4
19	8-Cl	H	CH_3	H	273[1)4)]	4
20	9-F	p-F	CH_3	H	285-287[1)]	4
21	H	H	$-CH_2-$	H	207-210[1)]	2, 3, 4
22	9-OCH_3	H	CH_3	H	251-252[1)]	2, 4
23	9-Cl	p-F	CH_3	H	294-296[1)4)]	4
24	9-Cl	p-Cl	CH_3	H	260-262[1)4)]	4
25	H	H	CH_3	CH_3	203-206[2)]	2, 4
26	9-Cl	p-F	CH_3	CH_3	268-270[1)]	4
27	9-F	p-F	$-(CH_2)_3COC_6H_4$-pF	H	195-198[2)]	3
28	9-F	p-F	$-(CH_2)_3CH(OH)C_6H_4$-pF	H	193-194[2)]	3

Ex.	R_1	R_2	R_3	R_5	m.p.	Analogous to Ex.
29	9-CH_3	p-CH_3	$-(CH_2-CH_2-O)_3H$	H	123-126[3]	3
30	9-CH_3	p-CH_3	$-(CH_2-CH_2-O)_2H$	H	125-127[5]	3
31	H	H		H	193-196[2)4]	3
32	H	m-SCH_3	CH_3	H		2,4
33	7-Cl	H	CH_3	H		4
34	7-OCH_3	H	CH_3	H		2, 4
35	8-OH	H	CH_3	H		5
36	9-Cl	m-Cl	CH_3	H		4
37	8-Cl	p-Cl	CH_3	H		4
38	7-Cl	H	H	H		1
39	8-OCH_3	H	H	H		1
40	9-Cl	m-Cl	H	H		1
41	8-Cl	p-Cl	H	H		1
42	H	H	C_2H_5	H	205-211[1]	3
43	9-F	p-F	$(CH_2)_2C_6H_4$-oCl	H	185-190[1]	3
44	9-CH_3	p-CH_3	$(CH_2)_3COC_6H_4$-pF	H	175-182[1]	3

For Examples 10 to 15 Rf-values following thin layer chromatography [dichloromethane/ethanol/25 % ammonia (90:9:1)]:

Examples 10-13 : Rf = 0.3

Examples 14 and 15: Rf = 0.45

The compounds of the invention exhibit pharmacological activity and are therefore indicated for use as pharmaceuticals, e.g. for therapy.

In particular the compounds exhibit neuroleptic activity as indicated in standard tests. For example, in one standard test an inhibition of spontaneous motor activity is observed in mice on p.o. administration of from about 1 to about 50 mg/kg animal body weight of the compounds in accordance with the principles of Caviezel and Baillod (Pharm. Acta Helv. (1958), 33, 465-484). Additionally, the compounds on administration to mice of from about 0.1 to about 10 mg/kg i.p. inhibit the hypermotility induced by 4,α-dimethyl-m-tyramine (H 77/77) in a test carried out according to the principles of C. Rüdeberg, Psychopharmacology, 59, 247-254, (1978). The compounds also increase the sleep phase II in the sleep/wake cycle in the rat on administration of from 2 to 20 mg p.o.

The compounds are therefore indicated for use as neuroleptic agents. For this use an indicated daily dosage is from about 25 to about 100 mg of the compounds, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 6 to about 50 mg or in sustained release form.

Furthermore, the compounds exhibit anti-depressant activity as indicated in standard tests, for example,

by an inhibition of tetrabenazine-induced catalepsy and ptosis in rats on administration of from 1 to 50 mg/kg i.p. of the compounds in accordance with the method described by Stille (Arzneimittel-Forsch. 1964, 14, 534).

The compounds are therefore indicated for use as anti-depressant agents. For this use an indicated daily dosage is from about 20 to about 100 mg of the compounds conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 5 to about 50 mg or in sustained release form.

Furthermore, the compounds exhibit anti-allergic activity, as indicated in standard tests. For example, according to the principles of J. Mota, Immunology, 7, 681, (1964), in the passive cutaneous anaphylaxis test (PCA test) in the rat the compounds are active in a dose of from about 0.1 to about 3.2 mg/kg p.o.

The compounds are therefore indicated for use as anti-allergic agents. For this use an indicated daily dosage is from about 0.5 to about 10 mg of the compounds, conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing from about 0.12 to about 5 mg or in sustained release form.

The compounds of the invention may be administered in pharmaceutically acceptable acid addition salt form. Such acid addition salt forms exhibit the same order of

activity as the free base forms. The present invention also provides a pharmaceutical composition comprising a compound of the invention, in free base form or in pharmaceutically acceptable acid addition salt form, in association with a pharmaceutical carrier or diluent. Such compositions may be in the form of, for example, a solution or a tablet.

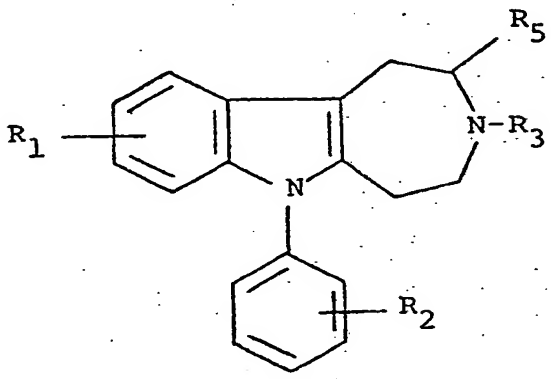
The neuroleptic activity is the preferred utility. The preferred compound is the Example 2 compound.

One group of compounds comprises compounds of formula I wherein R_1 and R_2 are independently hydrogen, halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy or trifluoromethyl, R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-5})alkenyl, (C_{3-5})alkinyl, or a group of formula II as defined above wherein either m is 3, X is CO and R_4 is fluorine in the para position or m is 1 or 2, X is a bond and R_4 is halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})alkoxy, or trifluoromethyl, and R_5 is hydrogen, with the proviso that, when one of R_1 and R_2 is hydroxy the other is hydrogen, halogen of atomic number from 9 to 35, (C_{1-4}) alkyl, hydroxy or trifluoromethyl.

What we claim is:-

1. 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b] indole, or an acid addition salt thereof.

2. An azepinoindol of formula I,

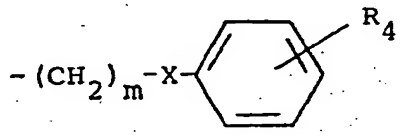


I

wherein

R_1 and R_2 are each independently hydrogen, halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})-alkoxy, (C_{1-4})alkylthio, hydroxy, or trifluoromethyl,

R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-6})cycloalkyl, (C_{4-9})-cycloalkylalkyl, (C_{3-5})alkenyl, (C_{3-5})alkinyl, a group of formula II,



II

wherein

m is 1, 2 or 3,

R_4 is halogen of atomic number from 9 to 35, (C_{1-4})-alkyl, (C_{1-4})alkoxy, or trifluoromethyl, and

X is a bond, -CHOH- or -CO-, or a group of formula III,

$-(CH_2-CH_2-O)_nH$ III

wherein

n is 2 or 3, and

R_5 is hydrogen or (C_{1-4})alkyl,

or an acid addition salt thereof.

3. A compound of claim 2 wherein R_1 and R_2 are, independently, hydrogen, halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})alkoxy, hydroxy or trifluoromethyl, R_3 is hydrogen, (C_{1-4})alkyl, (C_{3-5})alkenyl, (C_{3-5})alkinyl, or a group of formula II as defined above wherein either m is 3, X is CO and R_4 is fluorine in the para position or m is 1 or 2, X is a bond and R_4 is halogen of atomic number from 9 to 35, (C_{1-4})alkyl, (C_{1-4})alkoxy, or trifluoromethyl, and R_5 is hydrogen, with the proviso that when one of R_1 and R_2 is hydroxy the other is hydrogen, halogen of atomic number from 9 to 35, (C_{1-4})alkyl, hydroxy or trifluoromethyl.

4. A process for the production of a compound of claim 1 which comprises

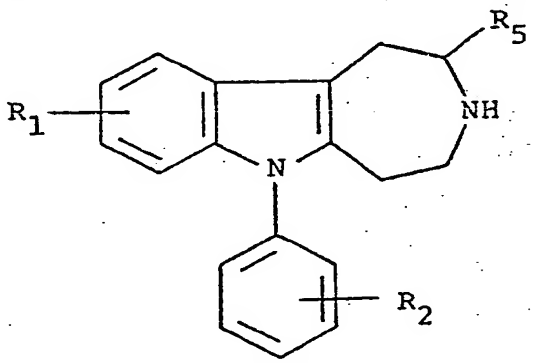
i) treating a 1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]-indole having a chloromethyl or bromomethyl group in the 1 position and unsubstituted on the nitrogen

atom in the 2 position, with a complex hydride to obtain a 1,2,3,4,5,6-hexahydro-6-phenyl-azepino [4,5-b]indole unsubstituted on the nitrogen atom in the 3 position, and, optionally,

ii) interconverting the 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b]indole into another 1,2,3,4,5,6-hexahydro-6-phenyl-azepino[4,5-b]indole.

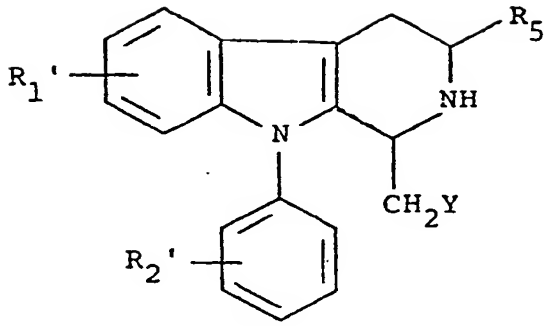
5. A process according to claim 4 for the production of a compound of formula I as defined in claim 2, which comprises

a) obtaining a compound of formula Ia,



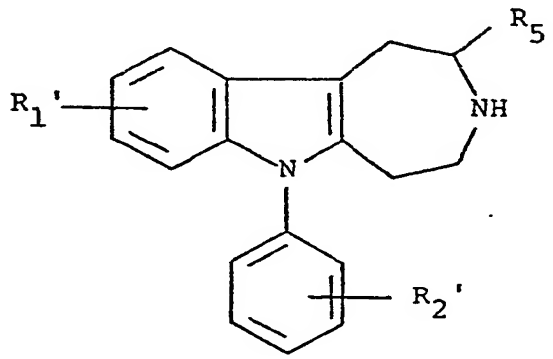
Ia

wherein R_1, R_2 and R_5 are as defined in claim 2, by enlarging the six-membered nitrogen containing ring of a compound of formula IV,



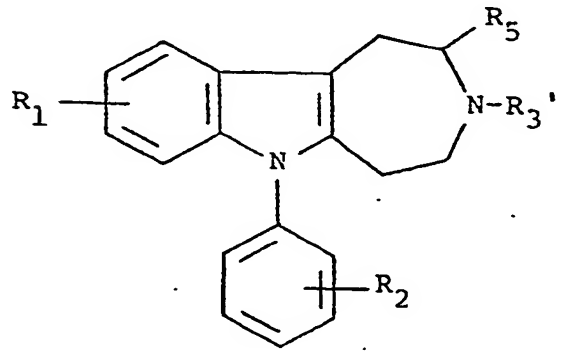
IV

wherein R_5 is as defined in claim 2 and R_1' and R_2' have the same significance as R_1 and R_2 except that any hydroxy group present is protected by a hydrogenolytically splittable group and Y is chlorine or bromine, and when at least one of R_1' and R_2' is a hydroxy group protected by a hydrogenolytically splittable group, hydrogenating the resulting compound of formula V,



V

b) obtaining a compound of formula Ib,



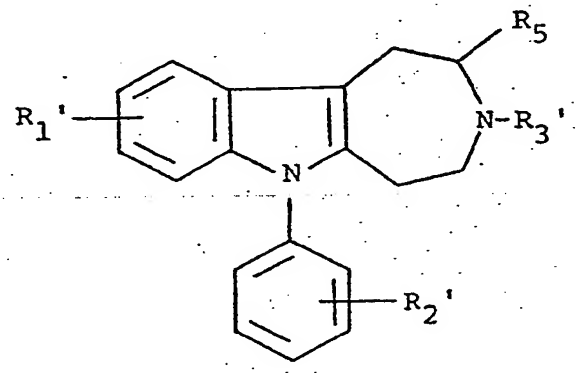
Ib

wherein

R_1, R_2 and R_5 are as defined in claim 2, and

R_3' is as R_3 with the exception of hydrogen,

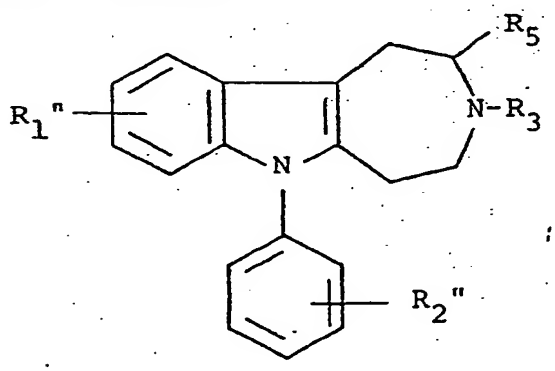
by introducing the group R_3' into a compound of formula V as defined above, and when at least one of R_1' and R_2' is a hydroxy group protected by a hydrogenolytically splittable group, hydrogenating the resulting compound of formula VI,



VI

or

c) obtaining a compound of formula Ic,



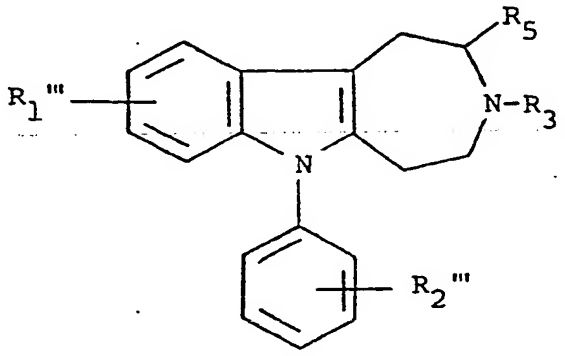
Ic

wherein

R_1" and R_2" have the same significances as R_1 and R_2 with the proviso that (i) none of them is an alkoxy group and (ii) at least one of them is a hydroxy group, and

R_3 and R_5 are as defined in claim 2, with the proviso that, when R_3 is a group of formula II, R_4 is other than alkoxy,

by subjecting a compound of formula VII,



VII

wherein

R_1"' and R_2"' have the same significances as R_1 and R_2 with the proviso that at least one of them is alkoxy,

R_3 and R_5 are as defined in claim 2, with the proviso that, when R_3 is a group of formula II, R_4 is other than alkoxy,

to an ether splitting.

6. A pharmaceutical composition comprising a compound of any one of claims 1 to 3 in association with a pharmaceutical carrier or diluent.

7. A compound of any one of claims 1 to 3 for use as a pharmaceutical.

8. A compound of any one of claims 1 to 3 for use as a neuroleptic, anti-depressant or anti-allergic agent.

9. A 1,2,3,4-tetrahydro-9-phenylpyrido[3,4-b]indole having a chloromethyl or bromomethyl group in the 1 position and unsubstituted on the nitrogen atom in the 2 position, or a compound of formula IV recited in claim 5.

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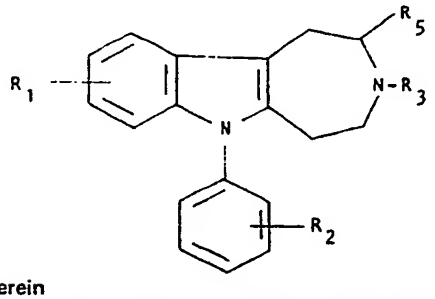
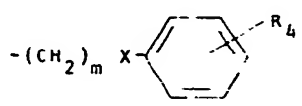
(54) **Azepinoindoles, process for their production and pharmaceutical compositions containing them, and intermediates.**

(57) Azepinoindoles of formula



wherein
R_1 and R_2 are hydrogen, halogen, alkyl, alkoxy, alkylthio, hydroxy, or trifluoromethyl,
R_3 is hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkinyl or a group of formula



wherein
m is 1, 2 or 3,
R_4 is halogen, alkyl, alkoxy, or trifluoromethyl, and alkyl, alkoxy, or trifluoromethyl, and
X is a bond, -CHOH- or -CO-,
or a group of formula

$$-(CH_2-CH_2-O)_nH$$

wherein
n is 2 or 3, and
R_5 is hydrogen or alkyl, are useful neuroleptic, anti-depressant and anti-allergic agents.

EP 0 028 381 A3

0028381

Application number

EP 80 10 6550

European Patent Office

EUROPEAN SEARCH REPORT

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
	US - A - 3 419 569 (GEIGY) * Claim 1; column 2, lines 28-69 *	2,6
	US - A - 3 839 357 (UPJOHN) * Column 2, lines 51-72; column 4, lines 1-21 *	2,6
	US - A - 3 553 232 (UPJOHN) * Claim 1; column 2, lines 31-37 *	2,6

CLASSIFICATION OF THE APPLICATION (Int. Cl.³)

C 07 D 487/04
A 61 K 31/55
C 07 D 471/04//
C 07 D 209/10
209/16
(C 07 D 487/04
223/00
209/00)
(C 07 D 471/04
221/00
209/00)

TECHNICAL FIELDS SEARCHED (Int.Cl.³)

C 07 D 487/04
A 61 K 31/55

CATEGORY OF CITED DOCUMENTS

X: particularly relevant
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: conflicting application
D: document cited in the application
L: citation for other reasons

&: member of the same patent family, corresponding document

~~The present search report has been drawn up for all claims~~

Place of search	Date of completion of the search	Examiner
The Hague	30.01.1981	ALFARO

EPO Form 1503.1 06.78

European Patent Office

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ All claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid,

namely claims:

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

X LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirement of unity of invention and relates to several inventions or groups of inventions,

namely: 1. Claims 1-8

2. Claim 9: Intermediates per se.

☐ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid,

namely claims:

☒ None of the further search fees has been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims,

namely claims: 1-8.